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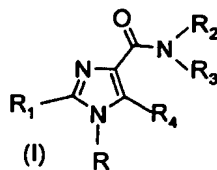
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(54) Title: 1H-IMIDAZOLE DERIVATIVES HAVING CB₁ AGONISTIC, CB₁ PARTIAL AGONISTIC OR CB₁-ANTAGONIS-
TIC ACTIVITY



(57) Abstract: AbstractThe present invention relates to a group of novel 1H-imidazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component. These 1H-imidazole derivatives are potent cannabinoid-CB₁ receptor agonists, partial agonists or antagonists, useful for the treatment of psychiatric and neurological disorders, as well as and other diseases involving cannabinoid neurotransmission. The compounds have the general formula (I) wherein R and R₁-R₄ have the meanings given in the specification.

1H-Imidazole derivatives having CB₁ agonistic, CB₁ partial agonistic or CB₁-antagonistic activity

5 The present invention relates to a group of novel 1H-imidazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

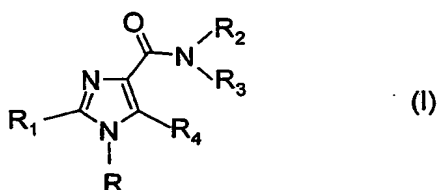
These 1H-imidazole derivatives are potent cannabinoid-CB₁ receptor agonists, partial agonists or antagonists, useful for the treatment of psychiatric and neurological disorders, as well as and other diseases involving cannabinoid neurotransmission.

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Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries (Mechoulam, R. and Feigenbaum, J. J. *Prog. Med. Chem.* **1987**, 24, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of cannabinoid receptors (CB₁ and CB₂) stimulated the search for novel cannabinoid receptor antagonists (Munro, S. *et al.*, *Nature* **1993**, 365, 61. Matsuda, L. A. and Bonner, T. I. *Cannabinoid Receptors*, Pertwee, R. G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system (Consroe, P. *Neurobiology of Disease* **1998**, 5, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, 1, 587. Greenberg, D. A. *Drug News Perspect.* **1999**, 12, 458. Pertwee, R.G., *Progress in Neurobiology* **2001**, 63, 569). Hitherto, several CB₁ receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB₁ receptor antagonists. A representative example is SR-141716A (Dutta, A.K. *et al.*, *Med. Chem. Res.* **1994**, 5, 54. Lan, R. *et al.*, *J. Med. Chem.* **1999**, 42, 769. Nakamura-Palacios, E. M. *et al.*, *CNS Drug Rev.* **1999**, 5, 43). CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB₁ receptor subtype-selective than SR141716A (Meschler, J. P. *et al.*, *Biochem. Pharmacol.* **2000**, 60, 1315). Aminoalkylindoles have been disclosed as CB₁ receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a moderately active CB₁ receptor antagonist, in some assays behaving as a weak partial agonist (Hosohata, K. *et al.*, *Life Sc.* **1997**, 61, PL115). Researchers from Eli Lilly described aryl-aryl substituted benzofurans as selective CB₁ receptor antagonists (e.g. LY-320135) (Felder, C. C. *et al.*, *J. Pharmacol. Exp. Ther.* **1998**, 284, 291). 3-Alkyl-5,5'-diphenylimidazolidine-diones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M. *et al.*, *Biorg. Med.Chem. Lett.* **1999**, 9, 2233). Aventis Pharma claimed diarylmethyleneazetidine analogs as CB₁ receptor antagonists (Mignani, S. *et al.*, Patent FR 2783246, 2000; *Chem. Abstr.* **2000**, 132, 236982). Tricyclic pyrazoles were claimed by Sanofi-Synthelabo as CB₁ antagonists (Barth, F. *et al.* Patent WO 0132663, 2001; *Chem. Abstr.* **2001**, 134, 340504). Interestingly, many CB₁ receptor

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- antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R. S. *et al.*, *Eur. J. Pharmacol.* **1997**, 334, R1). Pyrazole cannabinoids have also been reported as CB₁ receptor partial agonists showing *in vivo* cannabimimetic effects (Wiley, J. L. *et al.*, *J. Pharmacol. Exp. Ther.* **2001**, 296, 1013). A number of classes of CB₁ receptor agonists are known such as for example the classical cannabinoids (e.g. Δ^9 -THC), non-classical cannabinoids, aminoalkylindoles and eicosanoids (e.g. anandamide). Reviews provide a nice overview of the cannabinoid research area (Mechoulam, R. *et al.*, *Prog. Med. Chem.* **1998**, 35, 199. Lambert, D. M. *Curr. Med. Chem.* **1999**, 6, 635. Mechoulam, R. *et al.*, *Eur. J. Pharmacol.* **1998**, 359, 1. Williamson, E. M. and Evans, F. J. *Drugs* **2000**, 60, 1303. Pertwee, R. G. *Addiction Biology* **2000**, 5, 37. Robson, P. *Br. J. Psychiatry* **2001**, 178, 107. Pertwee, R. G. *Prog. Neurobiol.* **2001**, 63, 569. Goya, P. and Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, 10, 1529. Pertwee, R. G. *Gut* **2001**, 48, 859).
- It has now surprisingly been found that the novel 1H-imidazole derivatives of the formula (I), prodrugs thereof and salts thereof, are potent agonists, partial agonists or antagonists on cannabinoid-CB₁ receptors



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wherein

- R represents phenyl, thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl, which groups may be substituted with 1, 2, 3 or 4 substituents Y, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkoxycarbonyl, carboxyl, cyano, carbamoyl and acetyl, or R represents naphthyl, with the proviso that when R is 4-pyridinyl, R₄ represents a halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfonyl or branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or hydroxy group,
- R₁ represents phenyl or pyridinyl, which groups may be substituted with 1-4 substituents Y, which can be the same or different, wherein Y has the above mentioned meaning, or R₁ represents pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl, which groups may be substituted with 1-2 substituents Y, which can be the same or different or R₁ represents a five-membered aromatic heterocyclic ring having one or two heteroatoms from the group (N, O, S), which heteroatoms can

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be the same or different, which five-membered aromatic heterocyclic ring may be substituted with 1-2 substituents Y, which can be the same or different or R₁ represents naphthyl,

- 5 - R₂ represents H, branched or unbranched C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl which groups may contain a sulfur, oxygen or nitrogen atom,
- 10 - R₃ represents branched or unbranched C₂₋₈ alkyl, C₁₋₈ alkoxy, C₅₋₈ cycloalkyloxy, C₃₋₈ cycloalkyl, C₅₋₁₀ bicycloalkyl, C₆₋₁₀ tricycloalkyl, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl, which groups may optionally contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group or 1-2 C₁₋₃ alkyl groups or 1-3 fluoro atoms, or R₃ represents a benzyl or phenethyl group which aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkylsulfonyl, dimethyl-sulfamido, C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R₃ represents a phenyl or pyridinyl group, which groups are substituted with 1-4 substituents Z, wherein Z has the meaning as indicated above,
- 15 or R₃ represents a pyridinyl group, or R₃ represents a phenyl group, with the proviso that R₄ represents a halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl or C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or hydroxy group,
- 20 or R₃ represents a group NR₅R₆ with the proviso that R₂ represents a hydrogen atom or a methyl group, wherein
- 25 - R₅ and R₆ are the same or different and represent branched or unbranched C₁₋₄ alkyl, or R₅ and R₆ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic group having 4 to 10 ring atoms which heterocyclic group contains one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which heterocyclic group may be substituted with a C₁₋₃ alkyl group or a hydroxy group,
- 30 or R₂ and R₃ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic group having 4 to 10 ring atoms which heterocyclic group contains one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which heterocyclic group may be substituted with a C₁₋₃ alkyl group or a hydroxy group,
- 35 - R₄ represents a hydrogen or halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl or branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or a hydroxy group,
- 40 or R₄ represents a hydrogen or halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl or branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or a hydroxy group,

Due to the potent CB₁ agonistic, partial agonistic or antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, 5 appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, 10 plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, diabetes, cancer, emesis, nausea, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

15 The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB₁ receptor is stably transfected in conjunction with [³H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane 20 preparation with the [³H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

25 The cannabinoid CB₁ antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant 30 activation of CB₁ receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB₁ receptor-mediated response can be antagonized by CB₁ receptor antagonists such as the compounds of the invention.

35 Cannabinoid agonistic or partial agonistic activity of compounds of the invention can be determined according to published methods, such as assessment of *in vivo* cannabimimetic effects (Wiley, J. L. *et al.*, *J. Pharmacol. Exp. Ther.* 2001, 296, 1013).

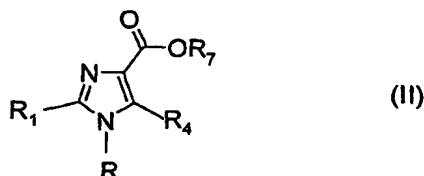
40 The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

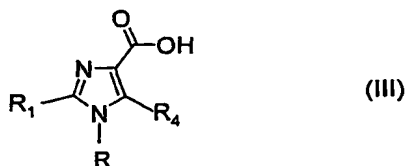
- 5 Suitable synthetic routes for the compounds of the invention are the following:

Synthetic route A

- 10 Step 1: ester hydrolysis of a compound having formula (II) wherein R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group



This reaction gives a compound having formula (III)



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wherein R , R_1 and R_4 have the meanings as described above.

Intermediates having formula (II), wherein R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group can be obtained according to methods known, for example:

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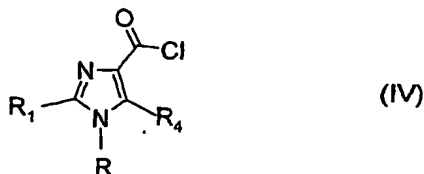
- a) I. K. Khanna et al., *J. Med. Chem.* **2000**, *43*, 3168-3185
- b) N. Kudo et al., *Chem. Pharm. Bull.* **1999**, *47*, 857-868
- c) K. Tsuji et al., *Chem. Pharm. Bull.* **1997**, *45*, 987-995
- d) I. K. Khanna et al., *J. Med. Chem.* **1997**, *40*, 1634-1647
- 25 e) M. Guillemet et al., *Tetrahedron Lett.* **1995**, *36*, 547-548

- 30 Step 2: reaction of a compound having formula (III) with a compound having formula R_2R_3NH wherein R_2 and R_3 have the meanings as described above *via* activating and coupling methods such as formation of an active ester, or in the presence of a coupling reagent such as DCC, HBTU, BOP or similar reagents. This reaction gives a desired 1H-imidazole derivative having formula (I).

(For more information on activating and coupling methods see: M. Bodanszky and A. Bodanszky: *The Practice of Peptide Synthesis*, Springer-Verlag, New York, 1994; ISBN: 0-387-57505-7).

Alternatively, a compound having formula (III) is reacted with a halogenating agent, for example thionyl chloride (SOCl_2). This reaction gives the corresponding carbonyl chloride (IV).

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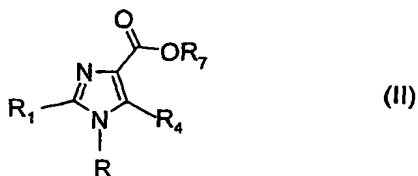


Reaction of a compound having formula (IV) with a compound having formula $\text{R}_2\text{R}_3\text{NH}$ wherein R_2 and R_3 have the meanings as described above, yields a 1H-imidazole derivative having formula (I). This reaction is preferably carried out in the presence of an organic base such as for example diisopropylethylamine (DIPEA) or triethylamine.

Alternatively, a compound having formula (II) is reacted in an amidation reaction with a compound having formula $\text{R}_2\text{R}_3\text{NH}$ wherein R_2 and R_3 have the meanings as described above to give a 1H-imidazole derivative having formula (I).

Synthetic route B

Reaction of a compound having formula (II), wherein R_4 represents hydrogen and wherein R , R_1 and R_7 have the meanings as described above for compound (II), with a compound having general formula $\text{R}_4'\text{-X}$, wherein X represents a leaving group and R_4' represents a C_{1-4} alkyl group, which alkyl group may be substituted with 1-3 fluoro atoms or wherein R_4' represents a cyano, formyl, acetyl, trifluoroacetyl, fluoroacetyl, methylsulfanyl or propionyl moiety, or a halogen atom. This reaction is carried out in the presence of a strong non-nucleophilic base such as lithium diisopropylamide (LDA), preferably under anhydrous conditions in an inert organic solvent, for example tetrahydrofuran, and yields a compound having formula (II)



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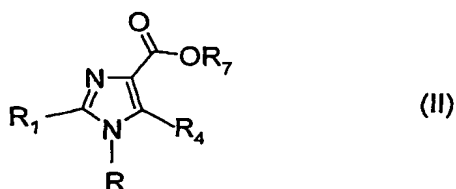
wherein R , R_1 and R_7 have the meanings as described hereinabove and R_4 represents a C_{1-4} alkyl group, which alkyl group may be substituted with 1-3 fluoro atoms or wherein R_4 represents a cyano, formyl, acetyl, trifluoroacetyl, fluoroacetyl, methylsulfanyl or propionyl group, or a halogen atom.

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Compounds of general formula (II) which have been obtained according to synthesis route B can be converted to compounds of general formula (I) analogously to the procedures described in synthesis route A, step 1 of route A or step 2 of route A (see
5 above).

Synthetic route C

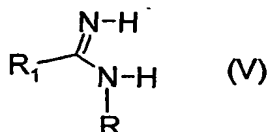
Compounds having formula (II)



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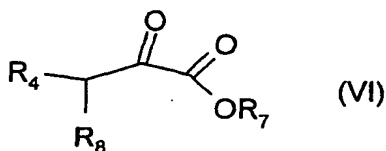
wherein R_4 represents a branched or unbranched C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro substituents and wherein R , R_1 have the meanings given above and R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group can be synthesized by reacting a compound having formula (V) or its tautomer

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wherein R and R_1 have the meanings given above, with a compound having formula (VI)

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wherein R_4 represents a branched or unbranched C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro atoms and R_8 represents a leaving group, for example a bromo substituent, and R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group. The reaction is preferably carried out in an organic solvent, for example in 2-propanol or in N-methyl-2-pyrrolidinone (NMP). The addition of an acid like trifluoroacetic acid (TFA) during the reaction may enhance the formation of the compounds having formula (II).

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(For more information on the leaving group concept see: M. B. Smith and J. March: *Advanced organic chemistry*, p. 275, 5th ed., (2001) John Wiley & Sons, New York, ISBN: 0-471-58589-0).

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Compounds of general formula (II) which have been obtained according to synthesis route C can be converted to compounds of general formula (I) analogously to the

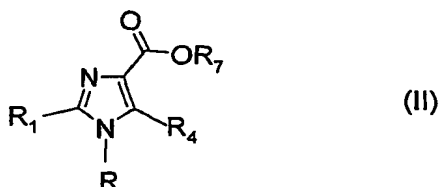
procedures described in synthesis route A, step 1 of route A or step 2 of route A (see above).

Compounds of the invention having formula (VI) can be obtained according to methods known, for example: P. Seifert *et al.*, *Helv. Chim. Acta*, 1950, 33, 725.

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Synthetic route D

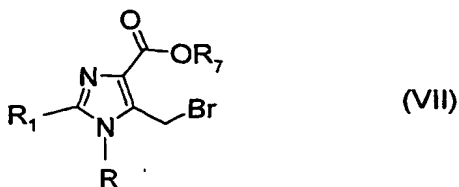
Reaction of a compound having formula (II)



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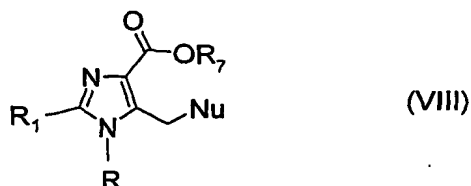
wherein R_4 represents a methyl group and R , R_1 have the meanings given above and R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group with a regioselective brominating compound such as N-bromo-succinimide (NBS) in an organic solvent such as CCl_4 in the presence of a free-radical initiator like dibenzoyl peroxide gives a compound of formula (VII)

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wherein R , R_1 and R_7 have the meanings given above. Reaction of a compound having formula (VII) (analogous to the method described in Mathews, W.B. *et al.*, *J. Label. Compds. Radiopharm.*, 1999, 42, 589) with for example KCl, KI, KF or KCN gives a compound of formula (VIII)

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wherein R , R_1 and R_7 have the meanings given hereinabove and Nu represents a chloro, iodo, fluoro or cyano group. The reaction is preferably carried out in the presence of a weak base like $NaHCO_3$ or in the presence of a crown ether or a cryptand. (For more information on crown ethers and cryptands see: M. B. Smith and

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J. March: Advanced organic chemistry, p. 105, 5th ed., (2001) John Wiley & Sons, New York, ISBN: 0-471-58589-0).

- 5 Compounds of general formula (VII) or (VIII) which have been obtained according to synthesis route D can be converted to compounds of general formula (I) analogously to the procedures described in synthesis route A, step 1 of route A, or step 2 of route A (see above).

Example 1

- 10 **Part A:** To a 1M solution of sodium bis(trimethylsilyl) amide in THF (70 mL) is added dropwise a solution of 4-chloroaniline (8.86 gram, 69.5 mmol) in anhydrous THF in a nitrogen atmosphere. After the mixture is stirred for 20 minutes a solution of 2,4-dichlorobenzonitrile (12 gram, 70 mmol) in THF is added. The resulting mixture is stirred overnight, poured into ice-water (400 mL) and extracted with dichloromethane,
15 dried over Na₂SO₄ and concentrated *in vacuo* to give a yellow oil (15.7 gram). Crystallisation from a dichloromethane/heptane mixture, and subsequent washing with methyl-t-butyl ether gives N-(4-chlorophenyl)-2,4-dichlorobenzenecarboxamidine (8.66 gram, 42 % yield) as a yellow solid. Melting point (MP): 93-95 °C.

- 20 Analogously was prepared:

– N-(4-bromophenyl)-2,4-dichlorobenzenecarboxamidine. MP: 117-119 °C.

- Part B:** A mixture of N-(4-chlorophenyl)-2,4-dichlorobenzenecarboxamidine (2.00 gram, 6.68 mmol), ethyl 3-bromo-2-oxopropanoate (2.65 gram, 13.6 mmol) and NaHCO₃ (1.12 gram, 13.3 mmol) in 2-propanol is stirred at reflux temperature for 20 hours. After cooling to room temperature the mixture is concentrated *in vacuo* and the residue suspended in dichloromethane, washed with water (3 x 50 mL) and brine (3 x 50 mL). The aqueous layers are extracted with dichloromethane. The combined
30 organic layers are dried over Na₂SO₄ and concentrated *in vacuo* to afford crude brown product (2.0 gram). This product is further purified by column chromatography (silicagel, heptane/EtOAc = 90/10 (v/v)) to yield ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (0.759 gram, 29 % yield) as a yellow oil which slowly solidifies on standing. Melting point: 150-152 °C; MS: 395 (MH⁺). ¹H-
35 NMR (400 MHz, CDCl₃): δ 7.91 (s, 1H), 7.49 (dd, J = 8 Hz, J = 2 Hz, 1H), 7.29-7.36 (m, 4H), 7.07 (dt, J = 8 Hz, J = 2 Hz, 2H), 4.44 (q, J = 7 Hz, 2H), 1.42 (t, J = 7 Hz, 3H).
Part C: Ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (0.810 gram, 2.06 mmol) and LiOH (0.173 g, 7.20 mmol) are dissolved in a H₂O/THF (20 mL/20 mL) mixture and stirred at 50 °C for 16 hours. The mixture is concentrated
40 *in vacuo* to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylic acid. Thionyl chloride (60 mL) is added and the mixture is heated at reflux

temperature for 1 hour and concentrated *in vacuo* to give crude 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carbonyl chloride.

Part D: Crude 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carbonyl chloride (919 mg, ~2.39 mmol), 1-aminopiperidine (0.469 g, 4.69 mmol) and triethylamine (0.363 g, 3.59 mmol) are dissolved in dichloromethane and stirred for one hour at room temperature. The mixture is washed with a saturated aqueous NaHCO₃ solution (3 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo* and further purified by column chromatography (ethyl acetate, silicagel) to give 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide (356 mg, 26 % yield (based on ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate). Mass Spectrometry (MS): 449.

Analogously were prepared:

2. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(pyrrolidin-1-yl)-1H-imidazole-4-carboxamide; MS: 435.
3. N-(t-Butoxy)-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide; MS: 438.
4. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-phenyl-1H-imidazole-4-carboxamide; MS: 442.
5. 1-(4-Chlorophenyl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide; MS: 448.
6. N-(Benzyl)-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-methyl-1H-imidazole-4-carboxamide; MS: 470.
7. 1-[1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-4-(1H-imidazolyl)carbonyl]hexahydro-1H-azepine; MS: 448.
8. 2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide (prepared from 2,4-dichloroaniline and 4-chlorobenzo-nitrile); MS: 449.
9. N-(t-Butoxy)-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide (prepared from 2,4-dichloroaniline and 4-chlorobenzonitrile); MS: 438.

Example 10

Part A: Diisopropylamine (2.30 gram, 22.8 mmol) is added dropwise to anhydrous THF (100 mL) in a nitrogen atmosphere at 0 °C. n-BuLi is added dropwise (7.34 mL, 2.5 M solution in hexane, 18.4 mmol). The resulting solution is cooled to - 78 °C. A solution of ethyl 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (6.0 gram, 15.2 mmol) in anhydrous THF is added dropwise. The colour of the mixture changes from yellow to purple brown. The stirred mixture is warmed to - 40 °C and cooled to - 78 °C and allowed to stand for 30 minutes. Methyl iodide (6.44 gram, 45.4 mmol) is added dropwise and the resulting solution is stirred for 30

min at - 78 °C and then allowed to attain room temperature. The resulting solution is quenched with an aqueous NH₄Cl solution, diethyl ether is added and the organic layer is dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil (6.4 gram). This oil is purified by column chromatography (toluene/EtOAc = 10/2 (v/v), silicagel) to give pure ethyl 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxylate (5.3 gram, 85 % yield) as a yellow oil.

Part B: Ethyl 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxylate (0.250 gram, 0.61 mmol) and LiOH (0.052 gram, 2.17 mmol) are dissolved in H₂O/THF (1:1 (v/v); 50 mL) and stirred at 50 °C for one hour. The mixture is concentrated to give crude 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxylic acid. To this mixture is added SOCl₂ (50 mL) and the resulting mixture is heated at reflux temperature for 1 hour. The mixture is concentrated to give 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbonyl chloride.

Part C: 2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbonyl chloride (1.5 gram, 3.75 mmol), 1-aminopiperidine (0.725 gram, 7.25 mmol) and triethylamine (0.549 gram, 5.44 mmol) are dissolved in dichloromethane and stirred for one hour at room temperature. The mixture is washed with a saturated aqueous NaHCO₃ solution, dried over Na₂SO₄ and concentrated *in vacuo* and further purified by column chromatography (heptane/ethyl acetate = 1/1 (v/v), silicagel) to give 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide (0.220 gram, 13 % yield) as a white foam. MS: 463.

Analogously were prepared:

11. N-(t-Butoxy)-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide: MS: 452.
12. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide: MS: 463; Melting point: 165-167 °C.
13. N-(t-Butoxy)-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-5-methyl-1H-imidazole-4-carboxamide: MS: 452.
14. N-(t-Butoxy)-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide: Amorphous. MS: 468.
15. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide: MS: 477.
16. 1-(4-Bromophenyl)-N-(t-butoxy)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide: Amorphous.
17. 1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide: MP: > 204 °C. TLC (Silicagel, EtOAc) R_f = 0.3.
18. 1-(4-Bromophenyl)-N-(t-butoxy)-2-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide: Amorphous. TLC (Silicagel, CH₂Cl₂/acetone = 9/1 (v/v)) R_f = 0.45.

19. 1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide: MP: > 140 °C. TLC (Silicagel, EtOAc) R_f = 0.4.
20. 1-(4-Bromophenyl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide: Melting point > 135-140 °C.
- 5 21. 1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(n-pentyl)-1H-imidazole-4-carboxamide: Syrup. TLC (Silicagel, CH₂Cl₂/acetone = 19/1 (v/v)) R_f = 0.4.

Example 22

10 **Part A:** To a stirred solution of ethyl 1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (6.10 gram, 0.0139 mol) in THF (70 mL) is added LiOH (0.67 gram, 0.0278 mol) and water (70 mL). The resulting mixture is stirred for 16 hours at 50 °C to give a clear solution. After cooling to room temperature, HCl (1N solution, 28 mL) is added to give an oily precipitate which completely solidifies on continued stirring and addition of water (70 mL). The precipitate is collected by filtration,

15 washed with water and dried *in vacuo* to give 1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylic acid (4.92 gram, 86 % yield). Melting point: 138-142 °C.

Part B: To a stirred suspension of 1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylic acid (1.23 gram, 2.99 mmol) in dry acetonitrile (40 mL) is successively added diisopropylethylamine (DIPEA) (1.15 mL, 6.6 mmol), O-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate (HBTU) (1.36 gram, 3.6 mmol) and 1-aminopiperidine (0.39 mL, 3.6 mmol). After stirring for 16 hours, the resulting mixture is concentrated *in vacuo*. The residue is dissolved in ethylacetate and an aqueous NaHCO₃ solution is added. The ethylacetate layer is

20 collected, washed with water and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a crude solid. This solid is further purified by recrystallisation from acetonitrile to give 1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide (830 mg, 56 % yield). Melting point: 219-221 °C.

30 Analogously were prepared:

23. N-(t-Butoxy)-1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide. Amorphous. TLC (Silicagel, Et₂O) R_f = 0.3.
24. 1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-N-(pyrrolidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 238-240 °C.
- 35 25. N-(Azepan-1-yl)-1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 201-204 °C.
26. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-1H-imidazole-4-carboxamide. MS: 475.
- 40 27. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(4-fluorobenzyl)-1H-imidazole-4-carboxamide. MS: 474.

28. 1-(4-Chlorophenyl)-2-(2-methoxy-4-chlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 220 °C.
29. 1-(4-Chlorophenyl)-N-cyclohexyl-2-(2-methoxy-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 177-179 °C.
- 5 30. 1-(4-Chlorophenyl)-2-(2-fluoro-4-chlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 217-218 °C.
31. 2-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 175-176 °C.
32. N-Cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide. Melting point: 184-185 °C.
- 10 33. N-Cyclohexyl-2-(2-fluoro-4-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 157-159 °C.
34. 1-(4-Chlorophenyl)-2-(2-methoxy-4-chlorophenyl)-N-(n-pentyl)-1H-imidazole-4-carboxamide. Melting point: 115 °C.
- 15 35. 2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 178-179 °C.
36. N-Cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide. Melting point: 175-176 °C.
37. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N,N-diethyl-1H-imidazole-4-carboxamide. Melting point: 177-179 °C.
- 20 38. 1-(4-Chlorophenyl)-N-cyclohexyl-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 172 °C.
39. 1-(4-Chlorophenyl)-N-(piperidin-1-yl)-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 219 °C.
- 25 40. N-(1-Adamantyl)-1-(4-chlorophenyl)-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 288 °C.
41. 1-(4-Chlorophenyl)-N-(2,2,2-trifluoroethyl)-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 149 °C.
42. 2-(2,4-Dichlorophenyl)-1-(pyridin-3-yl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 165-170 °C.
- 30 43. N-Cyclohexyl-2-(2,4-dichlorophenyl)-1-(pyridin-3-yl)-1H-imidazole-4-carboxamide. Melting point: 195 °C.
44. 2-(2,4-Dichlorophenyl)-1-(pyridin-3-yl)-N-(n-pentyl)-1H-imidazole-4-carboxamide. Melting point: 117 °C.
- 35

Example 45

Part A: 2,4-Dichlorobenzoyl chloride (40.0 g, 0.19 mol) is dissolved in tetrahydrofuran (1 L). To the resulting stirred solution is successively added diisopropylethylamine (DIPEA) (73.4 mL, 2.2 molar equivalent) and 4-(trifluoromethyl)phenylamine (30.7 g, 0.19 mol). After one hour the mixture is concentrated *in vacuo* to give an oil. This oil is crystallised from ethanol to give pure 2,4-dichloro-N-(4-(trifluoromethyl)phenyl)benzamide (53.2 g, 83 % yield). ¹H-NMR

40

(200 MHz, DMSO- d_6): δ 10.90 (br s, 1H), 7.91 (br d, J = 8 Hz, 2H), 7.63-7.77 (m, 4H), 7.57 (dt, J = 8 Hz, J = 2 Hz, 1H).

Part B: 2,4-Dichloro-N-(4-(trifluoromethyl)phenyl)benzamide (19.0 g, 0.057 mol) is dissolved in benzene (150 mL) and PCl_5 (13.0 g, 1.1 molar equivalent) is added. The resulting mixture is heated at reflux temperature for two hours, allowed to attain room temperature and concentrated *in vacuo* to give a residue. The residue is dissolved in anhydrous THF, cooled to 0 °C and transferred into an autoclave. Excess NH_3 is quickly added from a lecture bottle and the mixture is stirred at room temperature for 50 hours. A mixture of ethylacetate and aqueous $NaHCO_3$ is added. The ethylacetate layer is collected, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting oil is purified by column chromatography (diethyl ether/petroleum ether = 1/1 (v/v), silicagel) to give pure 2,4-dichloro-N-(4-(trifluoromethyl)phenyl)benzenecarboxamidine (16.9 g, 89 % yield). Melting point: 108-109 °C.

Part C: 2,4-Dichloro-N-(4-(trifluoromethyl)phenyl)benzenecarboxamidine (15.0 g, 0.0450 mol) is dissolved in 2-propanol and ethyl 3-bromo-2-oxobutanoate (20.8 g, 2 molar equivalent) and $NaHCO_3$ are successively added. The resulting mixture is heated at reflux temperature for 40 hours and allowed to attain room temperature. The 2-propanol is removed *in vacuo*, ethyl acetate is added to the residue and the resulting organic layer is washed with $NaHCO_3$ (5 % aqueous solution). The ethylacetate layer is collected, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting oil is purified by column chromatography (diethyl ether/petroleum ether = 1/3 (v/v), silicagel) and further purified by crystallisation from cyclohexane to give ethyl 2-(2,4-dichlorophenyl)-5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxylate (10.45 g, 52 % yield) as a yellow solid. Melting point: 160-162 °C.

Part D: The formed ethyl 2-(2,4-dichlorophenyl)-5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxylate is converted to 2-(2,4-dichlorophenyl)-5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxylic acid (melting point: 224-226 °C), which carboxylic acid is converted to 2-(2,4-dichlorophenyl)-5-methyl-N-(piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxamide (melting point: 173-174 °C) according to the procedure described in example 22 above. Analogously were prepared

46. 2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxamide. Melting point: >200 °C (decomposition).
47. N-Cyclohexyl-2-(2,4-dichlorophenyl)-5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxamide. Melting point: 178-179 °C.
48. N-Cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxamide. Melting point: 199-200 °C.

40 Example 49

Part A: N-(4-methoxyphenyl)-2,4-dichlorobenzenecarboxamidine (15.0 gram, 50.8 mmol) is dissolved in 2-propanol and ethyl 3-bromo-2-oxobutanoate (23.5 g, 2 molar

equivalents) and NaHCO_3 (8.5 gram, 2 molar equivalents) are successively added. The resulting mixture is heated at reflux temperature for 40 hours and allowed to attain room temperature. The 2-propanol is removed *in vacuo*, ethyl acetate is added to the residue and the resulting organic layer is washed with NaHCO_3 (5 % aqueous solution). The ethylacetate layer is collected, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting oil is purified by column chromatography (diethyl ether/petroleum ether = 1/3 (v/v), silicagel) to give ethyl 2-(2,4-dichlorophenyl)-5-methyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxylate (8.61 g, 42 % yield) as a solid. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ 7.33 (d, J = 8 Hz, 1H), 7.27 (d, J = 2 Hz, 1H), 7.18 (dd, J = 8 Hz, J = 2 Hz, 1H), 7.03 (dt, J = 8 Hz, J = 2 Hz, 2H), 6.85 (dt, J = 8 Hz, J = 2 Hz, 2H), 4.42 (q, J = 7 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H), 1.43 (t, J = 7 Hz, 3H).

Part B: To a stirred solution of ethyl 2-(2,4-dichlorophenyl)-5-methyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxylate (8.00 gram, 0.0198 mol) in THF (80 mL) is added LiOH (0.59 gram, 2 molar equivalents) and water (80 mL). The resulting mixture is stirred for 16 hours at 80 °C. After cooling to room temperature, HCl (2N solution, 12.3 mL) is added to give an oily precipitate. After addition of water and extraction with ethylacetate, the ethylacetate layer is collected, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue is crystallised from diisopropyl ether and dried to give 2-(2,4-dichlorophenyl)-5-methyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxylic acid (4.04 gram, 87 % yield) as a pale grey solid. Melting point: 189-191 °C.

Part C: To 2-(2,4-dichlorophenyl)-5-methyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxylic acid (1.00 gram, 2.65 mmol) in dry acetonitrile (25 mL) is successively added diisopropylethylamine (DIPEA) (1.02 mL, 2.2 molar equivalents), O-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluoro-phosphate (HBTU) (1.21 gram, 1.2 molar equivalents) and the resulting solution is stirred for 15 minutes. Cyclohexylamine (0.36 mL, 1.2 molar equivalents) is added. After stirring for 50 hours, the resulting mixture is concentrated *in vacuo*. The residue is dissolved in dichloromethane and an aqueous NaHCO_3 solution is added. The dichloromethane layer is collected, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue is further purified by column chromatography (gradient: dichloromethane => dichloromethane/methanol = 99/1 (v/v), silicagel) to give N-(1-cyclohexyl)-2-(2,4-dichlorophenyl)-5-methyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide (1.03 gram, 85 % yield). Melting point: 160-161 °C.

Analogously were prepared:

50. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N,N,5-trimethyl-1H-imidazole-4-carboxamide. Melting point: 101-104 °C.
51. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. MS: 464 (MH^+).

52. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-methyl-N-(4-morpholinyl)-1H-imidazole-4-carboxamide. MS: 466 (MH⁺).
53. N-(1-Azepanyl)-1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. MS: 478 (MH⁺).
- 5 54. 1-(4-Chloropyridin-2-yl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. MS: 463.
55. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-methyl-N-(n-pentyl)-1H-imidazole-4-carboxamide. MS: 451.
56. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-N-(4-fluorobenzyl)-5-methyl-1H-imidazole-4-carboxamide. MS: 489. Melting point: 123-126 °C.
- 10 57. 1-(4-Chlorophenyl)-N-cyclohexyl-5-methyl-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 212 °C.
58. 1-(4-Chlorophenyl)-5-methyl-N-(piperidin-1-yl)-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 165 °C.
- 15 59. 1-(4-Chlorophenyl)-2-(2-methoxy-4-chlorophenyl)-5-methyl-N-(n-pentyl)-1H-imidazole-4-carboxamide. Melting point: 131 °C.
60. 1-(4-Chlorophenyl)-2-(2-methoxy-4-chlorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: > 256 °C.
61. N-Cyclohexyl-1-(4-chlorophenyl)-2-(2-methoxy-4-chlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 201 °C.
- 20 62. 2-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 223-224 °C.
63. 2-(2,4-Dichlorophenyl)-5-methyl-1-(4-methoxyphenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: > 90 °C (decomposition).
- 25 64. N-Cyclohexyl-1-(4-fluorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 229-230 °C.
65. 1-(4-Chlorophenyl)-5-methyl-N-(n-pentyl)-2-(2-trifluoromethyl-4-chlorophenyl)-1H-imidazole-4-carboxamide. Amorphous.
66. 1-(4-Chlorophenyl)-2-(2-fluoro-4-chlorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 195 °C.
- 30 67. 1-(4-Chlorophenyl)-2-(2-fluoro-4-chlorophenyl)-5-methyl-N-(n-pentyl)-1H-imidazole-4-carboxamide. Melting point: 115 °C.
68. 1-(4-Chlorophenyl)-N-(cyclohexyl)-2-(2-fluoro-4-chlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 188 °C.
- 35 69. 1-(4-Chlorophenyl)-N-(cyclohexyl)-2-(1,5-dimethyl-1H-pyrrol-2-yl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 188-189 °C.
70. 1-(4-Chlorophenyl)-2-(1,5-dimethyl-1H-pyrrol-2-yl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 208-210 °C.
71. 2-(2-Chlorophenyl)-1-(3-fluorophenyl)-5-methyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 236-238 °C.
- 40 72. 2-(2-Chlorophenyl)-1-(3-fluorophenyl)-5-methyl-N-(n-pentyl)-1H-imidazole-4-carboxamide. Melting point: 97-102 °C.

73. 2-(2-Chlorophenyl)-N-cyclohexyl-1-(3-fluorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 180-182.5 °C.
74. 2-(2-Chlorophenyl)-1-(3-fluorophenyl)-N-(2-(4-fluorophenyl)ethyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 123.5-126 °C.
- 5 75. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 146 °C.
76. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(4-morpholinyl)-1H-imidazole-4-carboxamide. Melting point: 223 °C.
- 10 77. N-(1-Azepanyl)-1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide. Melting point: 177 °C.
78. 1-(4-Chloropyridin-2-yl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide. Melting point: 149 °C.
79. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(n-pentyl)-1H-imidazole-4-carboxamide. Melting point: Oil.
- 15 80. 1-(4-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-ethyl-N-(4-fluorophenylmethyl)-1H-imidazole-4-carboxamide. MP: amorphous.
81. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(hexahydrocyclopenta-[c]pyrrol-2(1H)-yl)-5-methyl-1H-imidazole-4-carboxamide. MP: 143-146 °C.
82. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-phenyl-1H-imidazole-4-carboxamide. Melting point: 91-95 °C.
- 20 83. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(tetrahydro-2H-pyran-2-yloxy)-1H-imidazole-4-carboxamide. Melting point: 128-133 °C.
84. N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 194-195 °C.
- 25 85. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(2-fluoroethyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 128-133 °C.
86. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(trans-4-hydroxycyclohexyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 160 °C (dec.).
87. 1-([1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazol-4-yl]carbonyl)-4-hydroxypiperidine. Melting point: Amorphous.
- 30 88. 1-([1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazol-4-yl]carbonyl)-1,2,3,4-tetrahydroisoquinoline. Melting point: 143-146 °C.
89. N-(Endo-bicyclo[2.2.1]hept-2-yl)-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 194-195 °C.
- 35 90. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-N-(4-fluorobenzyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 165-166 °C.
91. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(n-pentyl)-1H-imidazole-4-carboxamide. Oil.
92. N-(Azepan-1-yl)-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 147-149 °C.
- 40 93. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(pyrrolidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 205-206 °C.

94. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(morpholin-4-yl)-1H-imidazole-4-carboxamide. Melting point: 225 °C (dec.).
95. 2-(2,5-Dichlorophenyl)-5-methyl-1-phenyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 227 °C.
- 5 96. N-Cyclohexyl-2-(2,5-dichlorophenyl)-5-methyl-1-phenyl-1H-imidazole-4-carboxamide. Melting point: 236 °C.
97. N-Cyclohexyl-2-(2,4-dichlorophenyl)-1-(2,5-difluorophenyl)-5-ethyl-1H-imidazole-4-carboxamide. Melting point: 144-146 °C.
98. N-Cyclohexyl-2-(2,4-dichlorophenyl)-1-(2,5-difluorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 206-208 °C.
- 10 99. N-Cyclohexyl-2-(1,5-dimethyl-1H-pyrrol-2-yl)-5-ethyl-1-phenyl-1H-imidazole-4-carboxamide. Melting point: 195-196 °C.
100. N-Cyclohexyl-2-(2,5-dichlorophenyl)-5-ethyl-1-phenyl-1H-imidazole-4-carboxamide. Melting point: 198-199 °C.
- 15 101. 2-(2,5-Dichlorophenyl)-5-ethyl-1-phenyl-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 207-208 °C.
102. 1-(4-Chlorophenyl)-5-methyl-2-(3-methylpyridin-2-yl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 211-213 °C.
103. 1-(4-Chlorophenyl)-N-cyclohexyl-5-methyl-2-(3-methylpyridin-2-yl)-1H-imidazole-4-carboxamide. Melting point: 188-190 °C.
- 20 104. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(3-(trifluoromethyl)phenyl)-1H-imidazole-4-carboxamide. Melting point: 177 °C.
105. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(3-(trifluoromethyl)benzyl)-1H-imidazole-4-carboxamide. Melting point: 138-140 °C.
- 25 106. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(4-(trifluoromethyl)benzyl)-1H-imidazole-4-carboxamide. Melting point: 232 °C.
107. 1-(4-Chlorophenyl)-N-cyclopentyl-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 172 °C.
108. 1-(4-Chlorophenyl)-N-cycloheptyl-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide. Melting point: 154-156 °C.
- 30

Example 109

Part A: Ethyl 1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate is converted to ethyl 1-(4-bromophenyl)-5-chloro-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate analogously to a published procedure (N. Kudo et al., *Chem. Pharm. Bull.* **1999**, 47, 857-868) using excess of SO₂Cl₂ in dichloroethane at reflux temperature for 50 hours.

35

Part B: Ethyl 1-(4-bromophenyl)-5-chloro-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate is converted to 1-(4-bromophenyl)-5-chloro-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide (melting point: > 150 °C; R_f (Silicagel, EtOAc) ~ 0.35) analogously to the procedure described in example 22 above. ¹H-NMR (400 MHz, CDCl₃): δ 7.85 (br s, 1H), 7.52 (dt, J = 8 Hz, J = 2 Hz, 2H), 7.26-7.36

40

(m, 3H), 7.01 (dt, J = 8 Hz, J = 2 Hz, 2H), 2.85-2.92 (m, 4H), 1.72-1.80 (m, 4H), 1.40 – 1.44 (m, 2H).

Example 110

- 5 **Part A:** To a stirred solution of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylic acid (18.38 gram, 50 mmol) in toluene (200 mL) in a nitrogen atmosphere is added N,N-dimethylformamide di-tert-butyl acetal (50 mL) and the resulting mixture is heated at 80 °C for 4 hours. After cooling to room temperature the reaction mixture is concentrated and diethyl ether is added. The resulting solution is
10 twice washed with water, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue is crystallised from diisopropyl ether to give pure tert-butyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (10.35 gram, 49 % yield). Melting point: 179-181 °C.

Part B:

- 15 Lithium diisopropyl amide (LDA) (5.25 mL of a 2 M solution in THF, 0.0105 mol) is added dropwise to a cooled solution (-70 °C) of tert-butyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (4.24 gram, 0.010 mol) in anhydrous THF (80 mL) in a nitrogen atmosphere and the resulting mixture is stirred for one hour. A solution of p-toluenesulfonyl cyanide (1.88 gram, 0.011 mol) in anhydrous
20 THF (20 mL) is added dropwise and the resulting red solution is stirred for one hour at - 70 °C and then allowed to attain room temperature. Diethyl ether is added and the resulting solution is quenched with water and filtered over hyflo. The organic layer is collected and washed with water, dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil. This oil is purified by column chromatography (dichloromethane, silicagel) to give 3.4 gram of tert-butyl 1-(4-chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate. Recrystallisation from diisopropyl ether gave crystalline tert-butyl 1-(4-chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate (2.57 gram, 57 % yield). Melting point: 210-212 °C.

- 30 Analogously was prepared:

- Tert-butyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxylate. ¹H-NMR (400 MHz, CDCl₃): δ 7.38 (d, J = 8 Hz, 1H), 7.34 (dt, J = 8 Hz, J = 2 Hz, 2H), 7.27 (d, J = 2 Hz, 1H), 7.22 (dd, J = 8 Hz, J = 2 Hz, 1H), 7.03 (dt, J = 8 Hz, J = 2 Hz, 2H), 2.40 (s, 3H), 1.63 (s, 9H).

35

Part C:

- To a solution of tert-butyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5-cyano-1H-imidazole-4-carboxylate (2.57 gram, 5.73 mmol) in dichloromethane (40 mL) is added trifluoroacetic acid and the resulting solution is stirred at room temperature for 20
40 hours and concentrated *in vacuo*. The residue is crystallised from diisopropyl ether to give pure 1-(4-chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylic acid (1.95 gram, 87 % yield). Melting point: 200-202 °C (dec.).

Part D:

1-(4-Chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylic acid is converted to 1-(4-chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide in 60 % yield, analogously to the procedure described in example 22, part B herein above. Melting point: 231-233.5 °C.

5

Analogously were prepared:

111. 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-iodo-N-(piperidin-1-yl)-1H-imidazole-4-carboxamide. Melting point: 196-201 °C.

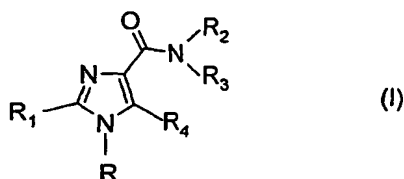
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112. 1-(4-Chlorophenyl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-5-iodo-1H-imidazole-4-carboxamide. Melting point: 226-230 °C.

113. 1-(4-Chlorophenyl)-5-cyano-N-cyclohexyl-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide. Melting point: 157-158 °C.

Claims

1. A compound of formula (I)



5

wherein

- 10 – R represents phenyl, thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl, which groups may be substituted with 1, 2, 3 or 4 substituents Y, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkoxycarbonyl, carboxyl, cyano, carbamoyl and acetyl, or R represents naphthyl, with the proviso that when R is 4-pyridinyl, R₄ represents a halogen atom or a
 15 cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl or branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or hydroxy group,
- 20 – R₁ represents phenyl or pyridinyl, which groups may be substituted with 1-4 substituents Y, which can be the same or different, wherein Y has the above mentioned meaning, or R₁ represents pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl, which groups may be substituted with 1-2 substituents Y, which can be the same or different or R₁ represents a five-membered aromatic heterocyclic ring having one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which five-membered aromatic heterocyclic ring may be
 25 substituted with 1-2 substituents Y, which can be the same or different or R₁ represents naphthyl,
- R₂ represents H, branched or unbranched C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl which groups may contain a sulfur, oxygen or nitrogen atom,
- 30 – R₃ represents branched or unbranched C₂₋₈ alkyl, C₁₋₈ alkoxy, C₅₋₈ cycloalkyloxy, C₃₋₈ cycloalkyl, C₅₋₁₀ bicycloalkyl, C₆₋₁₀ tricycloalkyl, C₃₋₈ alkenyl, C₅₋₈ cycloalkenyl, which groups may optionally contain one or more heteroatoms from the group (O, N, S) and which groups may be substituted with a hydroxy group or 1-2 C₁₋₃ alkyl groups or 1-3 fluoro atoms, or R₃ represents a benzyl or phenethyl group which
 35 aromatic rings may be substituted with 1-5 substituents Z, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkylsulfonyl, dimethyl-sulfamido, C₁₋₃-

alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R_3 represents a phenyl or pyridinyl group, which groups are substituted with 1-4 substituents Z, wherein Z has the meaning as indicated above,

- 5 or R_3 represents a pyridinyl group, or R_3 represents a phenyl group, with the proviso that R_4 represents a halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl methanesulfonyl, methylsulfanyl or C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or hydroxy group,
- 10 or R_3 represents a group NR_5R_6 with the proviso that R_2 represents a hydrogen atom or a methyl group, wherein
- R_5 and R_6 are the same or different and represent branched or unbranched C_{1-4} alkyl, or R_5 and R_6 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic group having 4 to 10 ring atoms which heterocyclic group contains one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which heterocyclic group may be substituted with a C_{1-3} alkyl group or a hydroxy group,
- 15 4 to 10 ring atoms which heterocyclic group contains one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which heterocyclic group may be substituted with a C_{1-3} alkyl group or a hydroxy group,
- 20 heterocyclic group contains one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which heterocyclic group may be substituted with a C_{1-3} alkyl group or a hydroxy group,
- R_4 represents a hydrogen or halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl or branched or unbranched C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro atoms or with a bromo, chloro, iodo, cyano or a hydroxy group,
- 25

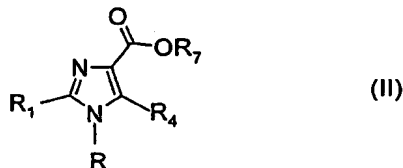
and prodrugs, stereoisomers and salts thereof.

- 30
2. Pharmaceutical compositions containing a pharmacologically active amount of at least one compound as claimed in 1 as an active component.
3. Method of preparing pharmaceutical compositions as claimed in claim 2
- 35 characterised in that a compound as claimed in claim 1 is brought in a form suitable for administration.
4. Process for the preparation of compounds having formula (I), characterised in that a compound is prepared wherein R , R_1 - R_3 have the meanings given in claim 1 and R_4 represents a hydrogen or halogen atom or a cyano, carbamoyl, formyl, acetyl, trifluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl or C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro atoms,
- 40

by reacting a compound having formula (II), (III) or (IV) with a compound of formula R_2R_3NH .

5. Process for the preparation of compounds having formula (II)

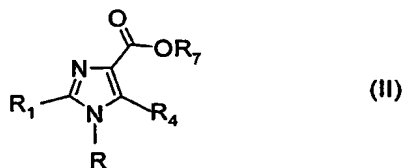
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10 wherein R_4 represents a C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro substituents, or wherein R_4 represents a halogen atom or a cyano, formyl, acetyl, trifluoroacetyl, fluoroacetyl, methylsulfanyl or propionyl group, characterized in that a compound is prepared wherein R and R_1 have the meanings given in claim 1 and R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group, by reacting a compound having formula (II) wherein R_4 is a hydrogen atom with a compound having formula $R_4'-X$, wherein X represents a leaving group and R_4' represents a C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro substituents, or wherein R_4' represents a halogen atom or a cyano, formyl, acetyl, trifluoroacetyl, fluoroacetyl, methylsulfanyl or propionyl group, in the presence of a strong non-nucleophilic base.

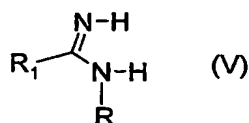
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6. Process for the preparation of a compound having formula (II)

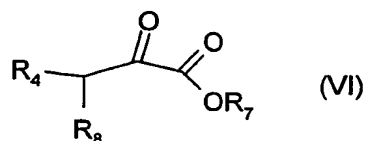


25 wherein R_4 represents a branched or unbranched C_{1-4} alkyl group, which C_{1-4} alkyl group may be substituted with 1-3 fluoro substituents, characterized in that a compound is prepared wherein R, R_1 have the meanings given in claim 1 and R_7 represents a branched or unbranched alkyl group (C_{1-4}) or benzyl group, by reacting a compound having formula (V) or its tautomer

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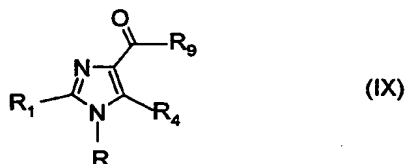


wherein R and R₁ have the meanings given in claim 1, with a compound having formula (VI)



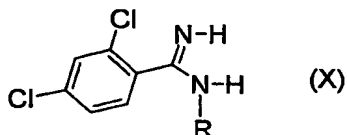
wherein R₄ represents a branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1-3 fluoro atoms and R₈ represents a so-called leaving group and R₇ represents a branched or unbranched alkyl group (C₁₋₄) or benzyl group.

7. Compounds of formula (IX)



wherein R and R₄ have the meanings given in claim 1 and wherein R₁ represents a phenyl or pyridinyl group, which groups are substituted with 1-4 substituents Y, which can be the same or different, or R₁ represents a pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl group, which groups are substituted with 1-2 substituents Y, which can be the same or different or R₁ represents a five-membered aromatic heterocyclic moiety having one or two heteroatoms from the group (N, O, S), which heteroatoms can be the same or different, which five-membered aromatic heterocyclic moiety may be substituted with 1-2 substituents Y, which can be the same or different or R₁ represents naphthyl and R₉ represents a hydroxy group, a branched or unbranched alkoxy (C₁₋₄) group, a benzyloxy group or a chloro substituent.

8. Compounds of formula (X) and tautomers thereof



wherein R represents a 4-chlorophenyl group, a 4-bromophenyl group or a 4-(trifluoromethyl)phenyl group.

9. Use of a compound as claimed in claim 1 for the preparation of a pharmaceutical composition for the treatment of disorders involving cannabinoid neurotransmission.

5

10. Use as claimed in claim 9 characterised in that said disorders are psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, 10 traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for 15 the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

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